

## PINEAL RESPONSE TO LITHIUM<sup>1</sup>

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### PINEAL FUNCTION AND BEHAVIOUR—A REVIEW

The pineal gland in man is an active endocrine gland throughout life (Wurtman *et al.*, 1964; Tapp & Huxley, 1972; Cardinali, 1974; Reiter *et al.*, 1975; Reiter, 1978). It elaborates several hormones with precise rhythmicity. The chronobiological aspects of the mammalian pineal gland have been clearly brought out by Reiter (1981) defining the circadian rhythms in indole metabolism within the pineal of mammals. The two major classes of pineal hormones—pineal indoles (melatonin, serotonin and the tryptophols) and the polypeptides are known to influence several physiological systems including the central nervous system (Cardinali, 1974 and Anton Tay, 1974). The association of pineal gland with behaviour and mental illness can be traced to Alexandrian school of thought (Herophilus c. 300 B.C.) that the pineal is a sphincter which regulates the flow of thought. Descartes (1650) located the soul, the origin of all thought in the pineal gland (quoted in Hunter and Macalpine, 1963). The first recorded post mortem at Bethlem Hospital by Thomas Allen in 1776 revealed that the pineal gland was “turned into a bladder of water” (Hunter and Macalpine, 1963). King (1686) observed that a mentally deranged patient, had a petrified pineal. Gunz (1753) suggested that concretions of pineal might be the cause of mania. This was supported by Morgagni (1769) and Arnold (1786). Assertions of a link between the pineal and insanity continued to appear in the eighteenth century

until Crowther demonstrated from his autopsy studies that pineal calcification had nothing to do with mental derangement.

Interest in the pineal gland lay dormant and the gland was relegated to be a vestigial organ until the endocrine nature of the gland was suggested following descriptions of pineal tumours associated with precocious puberty (Kitay, 1954). The idea of a special relation of pineal gland to mind was revived in reports of experiments with pineal extracts in the treatment of schizophrenia (Becker, 1920; Elderred *et al.*, 1960; Kitay & Altschule, 1954). The isolation and characterisation of the pineal hormone melatonin was a turning point in pineal research (Lerner *et al.*, 1958). Since then the pineal gland has been a focus of intense scientific enquiry revealing it to be an endocrine gland capable of affecting brain and behaviour.

Among the early observations on the influence of pineal gland on the brain are those of Quay (1965) on the inability of pinealectomised rats to maintain their cerebral potassium content. A slowing of brain maturation, particularly myelination was reported after pinealectomy in animals (Relkin *et al.*, 1973; Relkin & Schneck, 1975).

Pinealectomy is accompanied by a general increase in neural excitability (Nir *et al.*, 1969) and in stimulus-induced hippocampal potentials with convulsive patterns (Bindoni and Rizzo, 1965). Frank convulsions have been noted after pinealectomy in previously thyroparathyroidectomised ani-

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mals (Reiter and Morgan, 1972; Reiter *et al.*, 1972a). The convulsions result from changes in brain electrolytes and norepinephrine content (Reiter *et al.*, 1972; Reiter, 1977).

Administration of pineal extracts induces EEG activation (Quay and Renzoni, 1963; Roldan and Anton-Tay, 1968). Melatonin has powerful sedative effects on animals (Marceynski *et al.*, 1964; Barchas *et al.*, 1967; Hishikawa *et al.*, 1969). In human volunteers and in epileptics receiving melatonin an increase in alpha activity, EEG synchronisation and sleep, dreams, REM cycles, visual imageries and feelings of well-being have been observed (Anton Tay, 1971; 1972; Cramer *et al.*, 1976). In epileptics the paroxysmal discharges were suppressed by injections of melatonin (Anton-Tay *et al.*, 1971). Therapeutic benefits have been claimed with melatonin as an oral anticonvulsant (Anton Tay, 1974).

A well substantiated behavioural effect of melatonin is its ability to induce sleep (Barchas *et al.*, 1967; Marczynski *et al.*, 1964). Melatonin decreases the latency of sleep onset, of stages 3 and 4 and of REM sleep. The pattern of sleep induced strikingly resembles natural sleep (Cramer *et al.*, 1974, 1976). It facilitates barbiturate induced sleep (Martini, 1971). Koella (1969) has suggested that normal sleep may involve leakage of pineal hormones and their hyper-synchronising action via the area postrema, tractus solitarius and upper brainstem. Pineal arginine vasotocin (AVT) is reported to suppress REM sleep (Pavel *et al.*, 1977).

Following pinealectomy, dissociation develops between the nycthemeral variations of REM and slow-wave sleep. REM sleep decreases during the high phase of the cycle and increases during the dark phase (Anton Tay, 1972). In our studies, it was observed that following a 48-hour selective REM sleep deprivation, there was an increase in the NE and 5-HT fluo-

rescence in the rat pineal gland, signifying hyper activity (Parvathi Devi *et al.*, 1978).

Above all these facts, it has been found that plasma melatonin concentrations are high at night and low or absent during the day both in animals and men (Rollag & Niswender, 1976; Arendt *et al.*, 1977; Smith *et al.*, 1977; Kennaway *et al.*, 1977). In several recent studies of the temporal organization of melatonin concentrations during 24-hour periods in normal men, Weinberg *et al.* and Weitzman *et al.* have shown that although melatonin values are significantly higher at night during sleep, episodic secretion exists during the waking daytime period (Weinberg *et al.*, 1973; and Weitzman *et al.*, 1978).

Lewy *et al.*, (1979), who used a new mass spectroscopic assay, have found that the nocturnal secretion of melatonin from the pineal gland was substantially reduced during depressive phases compared to manic phases in bipolar cases. Since beta-adrenergic and serotonergic mechanisms mediate melatonin secretion, these observations could implicate disturbances in these neurotransmitter systems.

Recent studies suggest that certain depressed patients may have an altered biological rhythm. Alterations have been found in the sleep waking pattern timing of activity levels, diurnal mood variation and in the daily secretion of pituitary hormones as well as in other biological variables (Hawkins & Mendels, 1966; and Sachar, 1976). Since derangements of biological rhythm function have been linked with depression we considered it of interest to investigate the temporal organization of melatonin secretion in patients with unipolar and bipolar depression. The likely central nervous influence on melatonin secretion in man, its possible reflection of brain beta-receptor sensitivity (Hanssen, 1977) and the resemblance of its annual secretion pattern to that of hospital admission for depression (Eastwood and Peacocke, 1976) lead to the suggestion that

the study of rhythmic human melatonin secretion may prove to be of importance in diagnostic, prophylactic and therapeutic psychiatry. Of major importance in psychiatry are schizophrenia and manic-depressive disease which also for other reasons have been linked to a possible disturbance in pineal function (Altschule, 1975; and Carman *et al.*, 1976). Wattersberg, (1978) pointing disturbances in melatonin metabolism in schizophrenic and depressed patients and has suggested the possible use of melatonin excretion pattern as a predictive tool in the evaluation and outcome when treating depressed patients with sleep deprivation therapy. Mendlewicz *et al.* (1980) noting the 24 hour pattern of plasma melatonin in depressed patients before and after treatment indicated that the nocturnal melatonin increase found in normal subjects was essentially absent in 3 of the 4 depressed patients suggesting an altered pineal rhythm. The functional significance of the pineal in behaviour becomes very evident.

#### LITHIUM—ITS MODES OF ACTION—A REVIEW

Lithium sulfate was identified in 1817 by Arvedson, a young Swedish student of Chemistry and his celebrated teacher Berzelius. The elemental Lithium was isolated in 1855. Lithium is a soft white alkaline metal related to Sodium and Potassium. It is the lightest metal that can float in gasoline (Atomic number; 3, Atomic weight, 6.941, density; 0.531 g/cm.). The size of Lithium ions is larger than those of Sodium and Potassium but same as those of Magnesium. Chemically very reactive it never occurs in a free state in nature. There are two major source of Lithium, namely, the pegmatite and the brine deposits. Spodumene is the Lithium bearing ore in the pegmatite. The major mining operations are carried out in Kings Mountains and Bessemer city, North Carolina, United States. Though Lithium is

less abundant in the earth's crust than Sodium and Potassium it is known to be far more abundant than silver and Gold. Industrial and technological (textiles, ceramics, electronics, batteries, air-conditioners, enamel and glasses, aluminium) applications of Lithium exceed those of its medical use.

Lithium was introduced to Medicine by Lipowitz in 1841 and by Garrod in 1859 and to Psychiatry as an antimanic agent by Cade in 1949. After a period of lull, the Aarhus group of investigators in Denmark led by Schou added considerable knowledge of its use to make lithium one of the most important rediscoveries in psychiatric therapies.

The exact mechanism of action of lithium is not yet satisfactorily known. In the earlier days of its application, attention was directed to its effects upon electrolyte balance. Lithium can never act as a substrate for sodium though it replaces it and hence a failure in sodium pump mechanism occurs. The neuronal membrane is unable to maintain the polarization and conduct action potentials. However this is not likely in the clinical concentration of lithium in the blood. It was also advanced that lithium might correct a tendency for the intracellular concentration of sodium to increase in manic depressive psychosis as was proposed by Coppen and Shaw (1969). This theory appears untenable since the postulate that sodium is abnormally retained has not been established. In keeping with the monoamine hypothesis of affective disorders, lithium has been known to improve the manic episodes by preventing the release of NE (Katz *et al.*, 1968) and also to improve the reuptake (Coburn *et al.*, 1969). It also interferes with the development of supersensitivity of dopamine receptors in patients on chronic treatment with neuroleptics (Bunney, 1978). Lithium fails to offer support to the biogenic monoamine hypothesis of affective disorders with its uni-

directional amine effect and bidirectional clinical benefit. Lithium has been known to interfere with the action of the hormones including the transmitters on the adenylyl cyclase in the receptor function, it is particularly so in case of the thyroid. Lithium has been found to be antimanic and anti-thyroid, its antithyroid effect being a part of the antimanic effect (Whybrow, 1980). Wolpert (1975) emphasized the physiological factors in the genesis of recurrent affective disorders attributing mania to an excess of physiological energy, and its lack causing depression. Wolpert attributes the benefits of lithium to its normalizing effects upon the energy system. Other minor actions like the uptake and utilization of glucose, its action on magnesium have been resorted to explain its action (Frizel *et al.*, 1969; Carney *et al.*, 1973; and Srinivasan *et al.*, 1977).

Thus the role of lithium in the treatment of affective disorders has been extensively studied, its effects on ionic balance, on neurotransmitter dynamics and on endocrine mechanisms have also been documented (Cade, 1949; Schou *et al.*, 1954; Schou, 1957, 1958, 1966; Maletzky & Blachly, 1971; Platman & Fieve, 1968; and Schildkraut *et al.*, 1967). The influence of lithium on pineal gland activity as a possible mode of its therapeutic effect suggested itself to the present authors, who took note of the emergence of the pineal gland, in recent years, as a versatile neuro-endocrine transducer. It was then (1972), the outcome of a 'hunch' during investigations relating to the endocrine sequelae of lithium administration that the possibility of lithium evoking changes in the pineal gland was thought of by Parvathi Devi and the involvement of the pineal gland during lithium administration noted.

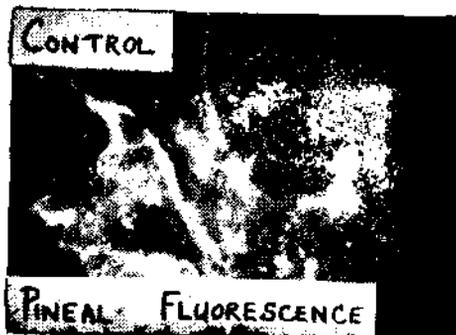
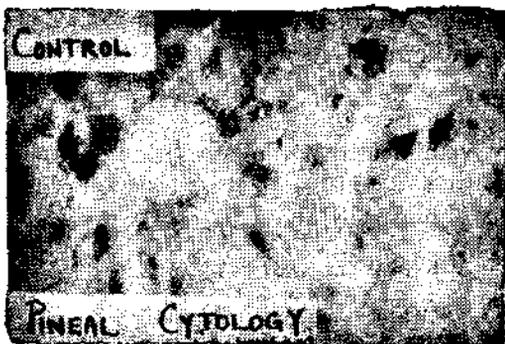
Lithium has been noted to mediate its action through the pineal-adrenocortical axis (Parvathi Devi *et al.*, 1973 and 1974). Further, it has been observed that lithium increased RNA synthesis, induced morpho-

logical changes of hyperactivity (Hariharasubramanian *et al.*, 1976). Increased NE and 5-HT fluorescence in the rat pineal gland was also evident. These effects were seen both in normal and adrenalectomised rats and were not abolished by exposure to constant illumination (Parvathi Devi *et al.*, 1976, 1977a, 1978a, 1978c and 1979). Lithium, like melatonin stabilises excitability of the brain (Johnson *et al.*, 1970; Small *et al.*, 1971) stimulates uptake of amines in the brain (Mendels and Frazer, 1974) and inhibits locomotor activity. It is suggested that the pineal hormones may mediate therapeutic and other systemic effects of lithium.

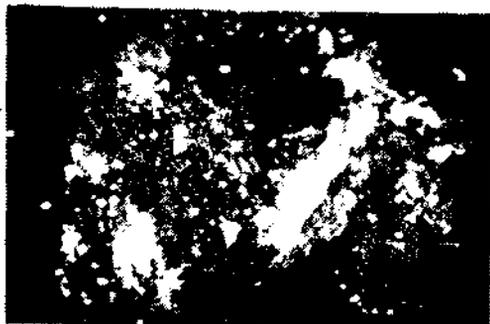
It is of interest to note that lithium and melatonin have similar actions on both the central nervous system and endocrines. Both stimulate uptake of biogenic amines in the brain (Mendels and Frazer, 1974), inhibit stimulus induced release of amines and induce EEG synchronization and sleep (Anton Tay *et al.*, 1971; Johnson *et al.*, 1970; and Small *et al.*, 1971). They suppress L-Dopa-induced hypermotility (Segal *et al.*, 1975; and Minneman & Wurtman, 1976), and inhibit thyroid function (Baschieri *et al.*, 1963; and Schou *et al.*, 1968). It seems quite possible to conclude that melatonin might mediate, at least in part, the therapeutic action of lithium and perhaps of other psychoactive drugs.

Within the pineal, norepinephrine stimulates synthesis and release of serotonin. The rhythm in pineal norepinephrine is abolished by depriving animals of light or by placing them under continuous illumination. When pineal norepinephrine is released, it causes a dramatic effect within the pinealocytes, stimulating the activity of pineal adenylyl cyclase. Exposure of experimental animals to continuous light reduces the activity of this enzyme. Serotonin (5-HT) rhythm within the pineal gland presents a circadian pattern. This rhythm is abolished exposure to constant

The Hyperactive Response of PINEAL to LITHIUM



LITHIUM TREATED HYPERACTIVE PINEAL



LITHIUM TREATED INCREASED PINEAL FLUORESCENCE

light, which also inhibits the pineal enzyme hydroxy indole-O-methyl transferase (HIOMT). HIOMT is responsible for the conversion of serotonin into melatonin. Constant lighting thus renders the pineal hypoactive.

The authors noted that the *lithium-mediated pineal stimulation* resulted in an increased serotonergic fluorescence within the pineals of normal and adrenalectomised rats on lithium administration, indicative of pineal responding to altered electrolyte balance. The pineals of lithium-treated rats also manifested increased serotonin content, the presence of serotonin being indicated by the development of yellowish-green 5-HT fluorophores. The authors also observed that the pineal hypo-activity induced by constant light was prevented when lithium was simultaneously administered an pineal hyperactivity was noted. This observation serves as an evidence of the pineal stimulatory response to lithium. Pineal responses to lithium point to an increased melatonin output.

#### *Pineal stimulatory response to lithium : 'TILAK EFFECT'*

A decade ago the idea that lithium could probably mediate pineal activity emerged (Parvathi Devi, 1972). Work in the direction of observing the effects of lithium on the pineal gland began. The findings evoked interest in several quarters. In July 1977 at the First British Lithium Congress at Lancaster, the authors had the opportunity to present the paper entitled "Lithium - Pineal - Adreno - cortical Axis." The late John F. Cade of Australia and Mogens Schou of Risskov, Denmark commented on the value of our observation on the *stimulatory response of the pineal gland to lithium* as very significant. They opined that while work on "the pineal gland" and "lithium" had been independently in progress, none hitherto had made a pointer to the "effects of lithium on the pineal gland."

*The stimulatory response of the pineal gland to lithium is christened "Tilak Effect."*

Effects similar to "Tilak Effect" have been under study with other psychoactive drugs (Parvathi Devi, 1982; Hariharasubramanian, 1982 and Srinivasan, 1982—unpublished observations).

Melatonin levels before and after lithium therapy in depressives are being studied and the value of the observations are being assessed for their therapeutic significance (Venkoba Rao *et al.*, 1982 and Parvathi Devi *et al.*, 1982)—(under publication).

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